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VERIFIED STATEMENT CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) & 1.27(c))—SMALL BUSINESS CONCERN

Docket Number (Optional)

Applicant or Patentee: Samuel Rose, M.D. (deceased June 3, 2001)
Application or Patent No.: SN08/782,590
Filed or Issued: 11/16/99
Title: A Method and Composition for the Treatment of Cancer by the Enzymatic Conversion of soluble radioactive toxic agents, etc.

I hereby declare that I am

- [X] the owner of the small business concern identified below:
- [ ] an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF SMALL BUSINESS CONCERN: ONCOLOGIC, INC.
ADDRESS OF SMALL BUSINESS CONCERN: 3065 Richmond Parkway, Suite 117
Richmond, California 94806

37 KD 8-28-01

I hereby declare that the above-identified small business concern qualifies as a small business concern as defined in 13 CFR 121.12, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees to the United States Patent and Trademark Office, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention described in:

- [X] the specification filed herewith with title as listed above.
- [X] the application identified above.
- [X] the patent identified above.

If the rights held by the above-identified small business concern are not exclusive, each individual, concern or organization having rights in the invention must file separate verified statements attesting to their status as small entities, and no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 CFR 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d), or a nonprofit organization under 37 CFR 1.9(e).

Each person, concern or organization having any rights in the invention is listed below:

- [ ] no such person, concern, or organization exists.
- [ ] each such person, concern or organization is listed below.

Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING: DAVID ROSE
TITLE OF PERSON IF OTHER THAN OWNER: Secretary and Treasurer, Oncologic, Inc.
ADDRESS OF PERSON SIGNING: 9552 Vallejo Street, Oakland, CA 94608
SIGNATURE: [signature] DATE: 7/30/01

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Date: November 27, 2000

JOHN Q. McQUILLAN

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12/15/00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT : SAMUEL ROSE, M.D.

SERIAL NO. : 08/782/590

FILED : January 13, 1997

FOR : A METHOD AND COMPOSITION FOR TREATING CANCER BY CONVERTING SOLUBLE RADIOACTIVE TOXIC AGENTS INTO INSOLUBLE RADIO - ACTIVE TOXIC PRECIPITATES VIA THE ACTION OF NON-MAMMALIAN ENZYMES BOUND TO THE NON-ENDOCYTOSING RECEPTORS OF TARGET CELLS

EXAMINER : Susan Ungar, Ph.D.

Group Art Unit : 1642

125 Crestwood Avenue
Tuckahoe, New York 10707

(914) 779-7171

Commissioner of Patents and Trademarks
Washington, D. C. 20231

LETTER

SIR:

This Letter is in response to the Official Action, mailed May 25, 2000.

REMARKS

Reconsideration and allowance of claims 69-83 are respectfully requested.

RESPONSES TO THE SECTIONS OF THE OFFICIAL ACTION

The following are submissions, comments, and arguments in response to the rejections by page numbers and line numbers of the Official Action, mailed May 25, 2000.

I. DECLARATIONS

Attached hereto are Declarations of Professor Emer. Henry Rapoport, Ph.D., dated May 24, 1999 and Dr. Alan Epstein, dated May 24, 1999 (submitted originally with the Preliminary Amendment, filed on November 16, 1999) and of Dr. George L. Mayers, dated November 27, 2000, each under 37 CFR, Section 1.132, traversing the grounds of rejection as identified by the section numbers of an Action recited therein.

IN THE CLAIMS:

Claim 69, line 25, delete "a period of time".

Claim 71, line 2, delete "molecule" and insert -- material --; and line 3, delete "molecule" and insert -- material --.

Claim 72, ine 2, delete "molecule" and insert -- material --; and line 3, delete "molecules" and insert -- materials --.

77. (three times amended) A therapeutic agent in accordance with claim 69 in which each of the indoxyl compounds can when attached to at least one of positions 4, 5, 6, and 7 of the indoxyl compound to [reduce the abiity of the indoxyl compoounds and the extra cellular precipitate to] move [by at least one of diffusion and convective flow] in the extracellular fluid.

78. (three times amended) A therapeutic agent in accordance with claim 69 in which each of the indoxyl compounds includes phenyl compounds attached at position 5 of the indoxyl compound to [reduce the ability of the indoxyl compounds and the extra-cellular precipitate to]move [by at least one of diffusion and convective flow] in the extracellular fluid.

79. (three times amended) A therapeutic agent in accordance with claim 69 in which each of the indoxyl compounds includes benzyloxy compounds attached at position 5 of the indoxyl compounds to reduce the abiity of the indoxyl compounds and the extra-cellular precipitate to move in the extracellular fluid.

Claims 69, 71, 72, and 77-79 have been amended to overcome the claim rejections under 35 U.S.C. Section 112.

Introduction

For clarification, this patent application describes a four-step process for the treatment f cancer:

1) In the first step, a first bispecific reagent, which consists of a non-mammalian first enzyme moiety plus a first targeting agent moiety for a non-endocytosing cell surface receptor which is somewhat cancer-specific, is administered to the living host. The first targeting agent moiety binds to the non-endocytosing receptors on cancer cells more than on normal cells, thereby retaining the non-mammalian first enzyme moiety in the extra-cellular fluid of cancer tissue more than normal tissue.
2) In the second step, a first therapeutic agent with antigenic epitopes is administered to the living host. The first therapeutic agent is converted by the action of the previously-bound first enzyme moiety into an insoluble non-digestible first extra-cellular precipitate with antigenic epitopes. The first therapeutic agent may be a) non-radiolabeled (Claim 69), in which case it is not therapeutic *per se* but rather serves only to become a non-radiolabeled first extra-cellular precipitate which is the site for subsequent therapeutic action, or b) radiolabeled (Claim 83), in which case it is therapeutic *per se* by becoming a radiolabeled first extra-cellular precipitate which is also the site for subsequent therapeutic action.
3) In the third step, a second bispecific reagent, which consists of a non-mammalian second enzyme moiety plus a targeting agent moiety specific for one of the antigenic epitopes on the first extra-cellular precipitate, is administered to the living host. The targeting agent moiety binds to one of the antigenic epitopes on the first extra-cellular precipitate, thereby retaining the non-mammalian second enzyme moiety in the extra-cellular fluid of the cancer tissue.
4) In the fourth step, an additional therapeutic agent, which is a soluble radioactive toxic agent, is administered to the living host. The second therapeutic agent is converted by the action of the previously-bound second enzyme moiety into a radioactive toxic new form capable of remaining in the extra-cellular fluid of the cancer tissue for an extended period of time sufficient to create radioactive Hot-Spots which kill non-selectively all (mostly cancer) cells adjacent to them.

OBJECTIONS

Paper 27, page 2, line 14-19

"Applicant argues that pages 14-16 contain a description of each of the drawing of Figures 1-44. The argument has been noted but has not been found persuasive because a review of the specification revealed that there is not an adequate description of each drawing. For example, the drawings are replete with numbers (for example, see Figure 36) which are not defined or described in any way in the Brief Description of the Drawings.

Response:

It is submitted that the Brief Description of the Drawings on pages 14-16 of the specification is in complete compliance with 37 § C.R.F.§ 1.74 and MPEP § 608.01(f):

1.74 Reference to drawings

> "When there are drawings, there shall be a brief description of the several views of the drawings and the detailed description of the invention shall refer to the different views by specifying the numbers of the figures and to the different parts by use of reference letters or numerials (preferably the latter)."

Furthermore, the detailed description of the invention beginning on page 17 of the specification completely conforms to the requirement of 37 C.F.R.§ 1.71 and MPEP § 608.01 in that each reference numeral and each drawing is specifically and completely identified and described in the specification.

Again contrary to what is indicated by the Examiner, there is no requirement in the USPTO Rules that the Brief Description of the Drawings recite details of what is set forth in the given drawing and certainty does not require that the Brief Description of the Drawings include a listing of the reference numeral set forth in the specification with respect to the particular drawing under consideration. In any event, a response to Section 4 of the current Action can be made by suitable amendments to the Brief Description of the Drawings on pages 14-16 of the Application.

CLAIM REJECTIONS

Paper 27, pag 4, line 4-13

"... (a') general methods of indoxyl chemistry, preparation of precipitable material and methods of radio labeling have been taught but the specification does not provide guidance on or exemplification of making or using the broadly claimed agents that would be therapeutic when administered *in vivo* and Applicant admits on the record that the therapeutic agent is only therapeutic after conversion. Without working examples that demonstrate that the conversion takes place *in vivo* which would provide guidance to one skilled in the art, given the issues raised in Paper No. 10, one of skill in the art could not predict that the therapeutic agent taught could be used with a reasonable expectation of success."

Paper 27, page 4, line 14-17

"... (c') Applicant is claiming a therapeutic agent, not a method for the conversion of a pro-drug to a therapeutic agent. Applicant admits on the record that the claimed therapeutic agent is not therapeutic *per se*."

Paper 27, page 5, line 16-20

"It is clear that, in the absence of objective evidence, Dr. Epstein cannot predict that the therapeutic agent will function as claimed and for the reasons previously set forth, that it cannot be predicted, in the absence of *in vivo* working examples, that the claimed therapeutic agent will function as claimed."

Paper 27, page 6, line 15-17

"Although the specification teaches how to make the soluble precipitable material cell impermeant, the specification does not teach how to use the therapeutic agent..."

Paper 27, page 6, line 21-22

"... the specification does not teach how to use the invention."

Paper 27, page 8, line 5-6

"... in the absence of objective evidence, in view of the known unpredictability of the cancer therapeutic arts, it could not be predicted that the claimed therapeutic agent would function as claimed."

Paper 27, page 8, line 8-10 and again on page 8, line 13-15

"... the issue raised here is not that a molecule cannot be made impermeant, but rather that the specification does not teach how to use the claimed molecule so that it will function as claimed."

Paper 27, page 8, line 21 – page 9, line2

"Applicant argues that the therapeutic agent is radioactive and therefore must cause some cell damage. The arguments have been considered but have not been found persuasive because applicant is arguing limitations not recited in the claims as presently constituted."

Response 1:

The introduction of this response presented concisely the 4-step method of the claimed invention. The first therapeutic agent is converted into the first extra-cellular precipitate by the enzyme moiety of the first bispecific reagent which is bound by the first targeting agent moiety of the first bispecific reagent to the first antigenic receptor of the first target cancer cells. Continued administration of the first therapeutic reagent results in the accumulation of a large amount of first extra-cellular precipitate in the extra-cellular fluid adjacent to the first target cancer cells. The first extra-cellular precipitate has at least one of a first antigenic eptitope, second antigenic epitope, and a neo-antigenic third epitope. Thus the accumulation of the first extra-cellular precipitate is also an accumulation of the first antigenic eptitope, second antigenic epitope, and neo-antigenic third epitope. The function of the non-radiolabeled first therapeutic agent as per Claim 69 is not to kill cancer cells (i.e. it is not therapeutic *per se*), but rather to accumulate the first extra-cellular precipitate which is used as the site for the subsequent therapeutic attack

delivered by the additional therapeutic agent. However, if the first therapeutic agent is radiolabeled as per Claim 83, it is therapeutic *per se* as well as serving to accumulate the first extracellular precipitate as the site for subsequent therapeutic attack delivered by the additional therapeutic agent.

The specification and the claims enable the present invention to be practiced by one of skill in the art. The specification and references for ADEPT (Publication Exhibits A and G-J, page 36, submitted with the response filed May 25, 1999) provide sufficient guidance for doses and methods of administration for the first bispecific reagent, the first therapeutic agent, and the second bispecific reagent to enable one of skill in the art to practice the present invention. In addition, the treatment of thyroid cancer with radio-iodide in particular, as well as the treatment of cancer using radio-labeled antibodies and the delivery of the pro-drug in ADEPT, provides sufficient guidance to one of skill in the art for doses and methods of administration of the radioactive toxic additional therapeutic agent to enable one of skill in the art to practice the present invention.

The well-published literature of ADEPT (which teaches the conversion of a pro-drug to an active drug by the enzyme moiety of a previously bound bispecific reagent) provides a valid working example for the present invention in which the first therapeutic agent is converted to the first extra-cellular precipitate by the enzyme moiety of the previously bound first bispecific reagent. Even in the absence of *in vivo* working examples, the disclosure in the specification of the present invention enables one of skill in the art to predict with high expectation of success, and without undue experimentation, that the first extra-cellular precipitate will form from the first therapeutic agent via the action of the first enzyme moiety of the first bispecific reagent, and that the first extra-cellular precipitate formed from the first therapeutic agent will accumulate in the extra-cellular fluid and will function as described. (For evidence that the insoluble precipitate will be removed by convection and phagocytosis slower from tumor tissue than for normal tissue, and thus one skilled in the art is able to successfully predict that the first therapeutic agent will be retained for an extended period of time in tumor tissue and therefore function as disclosed in the present invention, please see Response 4 below.)

Furthermore, Applicant has unpublished *in vitro* data produced by an independent third party (Marin Biologic of Tiburon, California) demonstrating that an immobilized enzyme (beta-galactosidase on beads in either phosphate-buffered saline or 1% agarose) converted the soluble precipitable material 4-chloro-3-indolyl-beta-D-galactopyranoside (akin to the first therapeutic agent of the present invention) to an insoluble indigo precipitate.

The following sample calculation illustrates how the specification and references for the working example of ADEPT, plus the working example of the 90%-curative treatment of thyroid cancer by the administration and immobilization of radio-iodide, provide sufficient guidance to one of skill in the art for doses and methods of administration of the first bispecific reagent, first therapeutic agent, second bispecific reagent, and radioactive toxic additional therapeutic agent of the present invention:

(1) Re: the current 90%-curative treatment of thyroid cancer with radio-iodide for 10 grams of tumor:

An attempt is made to accumulate 10(4) -- that is, ten thousand -- Iodine-131 atoms per cancer cell. This translates to 3x10(14) isotope atoms per 10 grams of tumor {10 grams X 3x10(9) cells per gram X 10(4) isotope atoms per cell}. The isotopes circulates with a biological half-life of approximately 3-10 hours (10 hours is used for these calculations) and remains in the tumor with a biological half-life of 1-3 days (3 days is used for the calculations). A low test dose of isotope and measuring thyroid uptake and blood levels determines the required therapeutic dose of isotope; there is NO standard uniform therapeutic dose which is used.

(2) Re: the present invention for 10 grams of tumor:

(a) 10 grams of tumor contain 3x10(9) cells.

(b) There are 10(4)-10(5) non-endocytosing receptors per cell {10(5) receptors per cell is used for these calculations}.

(c) Multiplying (a) X (b), there are 3x10(14) non-endocytosing receptors per 10 grams of

tumor.

(d) Approximately 1% {10(-2)} of the administered dose of an antibody targeting agent binds to 10 grams of tumor.

(e) Using (c) and (d), 3x10(16) {= 3 x10(14) X 10(2)} (antibody) first targeting agent moiety molecules must be administered to bind one molecule to each non-endocytosing receptor.

(f) Since each first targeting agent moiety molecule has attached to it one non-mammalian first enzyme moiety molecule (forming the first bispecific reagent), there will be 3x10(14) first enzyme moiety molecules bound per 10 grams of tumor after the bispecific reagent has been administered and allowed to bind to the non-endocytosing receptors.

(g) The turnover number of the first enzyme moiety (= rate of enzyme conversion of substrate into product) is approximately 10(2) per second or more.

(h) Since there are approximately 10(5) seconds per day, 3x10(14) first enzyme moiety molecules will convert 3x10(21) first therapeutic agent molecules to first extra-cellular precipitate molecules per day {3x10(14) first enzyme moiety molecules X 10(5) seconds per day X 10(2) per second turnover number of enzyme}. Thus, after administering the first bispecific reagent followed by the first therapeutic agent, there will be 3x10(21) molecules of insoluble non-digestible first extra-cellular precipitate with antigenic epitopes per 10 grams of tumor. {Note that if the first therapeutic agent is radio-labeled as per Claim 83, then 3x10(21) radioactive first extracellular precipitate molecules will be retained per 10 grams of tumor}.

(i) Following the reasoning above, the second bispecific reagent (which consists of a targeting agent moiety specific for one of the antigenic epitopes on the first extra-cellular precipitate plus a non-mammalian second enzyme moiety) is administered in sufficient quantity to bind one molecule of it to each molecule of first extra-cellular precipitate (via the antigenic epitopes on the precipitate).

(j) 3x10(21) second enzyme moiety molecules will convert 3x10(26) molecules of soluble radioactive additional therapeutic agent to the radioactive toxic new form per day {= approximately 1.5 x10 (26) molecules per 10 hours for comparison to the thyroid cancer treatment model in (1) above}, and the radioactive toxic new form will remain in

the extra-cellular fluid of the tumor with a biological half-life of at least 3 days (this is a conservative estimate and is the same as the biological half-life in the thyroid cancer model described above).

Thus the present invention has the potential to deposit and retain 5x10(11) times as many radioactive molecules in the tumor than does the 90%-curative treatment of thyroid cancer with radio-iodide {1.5x10(26) molecules versus 3x10(14) molecules}.

In actual practice, the number of isotope atoms deposited in the present invention is likely to be less than 1.5x10(26) per 10 hours because of a number of factors such as (a) steric hindrance, (b) macrophage uptake and convective flow into lymphatics of the first extra-cellular precipitate and the radioactive toxic new form, (c) endogenous antibody molecules which bind to the cell receptors and therefore compete with the administered first bispecific reagent, (d) complexing of the first targeting agent moiety of the first bispecific reagent with soluble cell receptors in the circulation, such complexes being quickly engulfed by macrophages of the liver, lung and spleen, and (e) loss of bispecific reagent bound to the receptors over time.

However, the huge potential excess of radioactive molecule deposition compared to thyroid cancer treatment (combined with the conservative estimate of the retention time of the radioactive toxic new form in the tumor, and the short duration of time necessary for the isotope to circulate in the blood) should enable the present invention to achieve micro-regional destruction of tumor cells with minimal systemic radioactive toxicity.

See also Mayers declaration.

Paper 27, page 4, line 13-14

"... (b') applicant is arguing limitations not present in the claims as currently constituted as immobilization of a radioisotope is not claimed."

Paper 27, page 4, line 17-1

"... (d') applicant is arguing limitations not recited in the claims as presently constituted as the claims are not drawn to immobilized radio-isotope atoms."

Response 2:

The introduction of this response presented concisely the 4-step method of the claimed invention, including how the first therapeutic agent is used principally to generate a non-toxic first extra-cellular precipitate as the site for the subsequent therapeutic attack delivered by the additional therapeutic agent. Independent claim 69 discloses the composition of the first therapeutic agent, and dependent claim 83 is a limitation of claim 69 wherein the first therapeutic agent is radio-labeled. Using a radio-labeled first therapeutic agent is claimed in the present invention and is disclosed in the specification. including methods of radio-labeling (page 23). The conversion of a radio-labeled first therapeutic agent would result in the formation of a radio-labeled first extra-cellular precipitate. Since the first extra-cellular precipitate is insoluble and therefore remains in the extra-cellular fluid for an extended period of time, the present invention does in fact claim the immobilization of a radioisotope. (Applicant also claims immobilization of a radioisotope when the second therapeutic agent is converted to the radioactive toxic new form.)

Paper 27, page 4, line 19 – page 5, line 6

"... (e') it is clear that the limitation that the therapeutic agent is not a protein is not recited in the claims as presently constituted and further, other than claim 83, none of the claims are drawn to radio-labeled soluble precipitable material and none of the claims are drawn to immobilized reagents. Without working examples, in view of the issues raised in Paper No. 10, one of skill in the art could not predict that the only location where the therapeutic agent will be immobilized will be at the site of the bispecific reagent, (f') the issue raised here was not that the specification does not describe protein and peptides as candidates for the soluble precipitable material but that Applicant's response was confusing because Applicant states on the record that the specification does not describe proteins and peptides as candidates for the soluble precipitable material."

Response 3:

The Examiner is correct that Applicant's response that "The therapeutic agent is not a protein ..." was confusing, in light of Claim 69 which states "... the first therapeutic agent comprising at least one organic chemical of at least one of peptides, including opio-melanins ..." The response should have stated that "The therapeutic agent is not a readily degradable protein ..." and proteolytic degradation is, therefore, not relevant. Certain peptides such as prion proteins, amyloid of Alzheimer's disease, and keratins are quite non-degradable. In the case of the named opio-melanins, although the peptide portion may be degradable, the remaining melanin portion is quite non-degradable.

Regarding claims drawn to immobilized reagents, please see Response 2 above.

Regarding the location where the therapeutic agent will be immobilized, as disclosed in the claims and specification of the present invention (Specification, page 17, 19-24), the conversion of the first therapeutic agent can only occur via the action of the first enzyme moiety of the first bispecific reagent. The conversion of the first therapeutic agent into the insoluble first extracellular precipitate by the first enzyme moiety of the previously bound first bispecific reagent is analogous to the prior art of ADEPT wherein a soluble prodrug is converted by the enzyme moiety of a previously bound bispecific reagent into an active drug (Specification, p. 9-10 and Publication Exhibits for ADEPT (A and G-J) submitted with the response filed May 25, 1999, page 36). Just as the pro-drugs of ADEPT are adapted to be converted to active drugs only by the enzyme moiety of the previously bound bispecific reagent, so the first therapeutic agent of the present invention is adapted to be converted to the first extra-cellular precipitate only by the first enzyme moiety of the previously bound first bispecific reagent. Thus, even in the absence of *in vivo* working examples, the disclosure in the specification enables one of skill in the art to predict that the only location where the first therapeutic agent will be immobilized will be at the site of the first enzyme moiety of the first bispecific reagent, because that is the only location at which the first therapeutic agent will be converted into the insoluble first

extra-cellular precipitate and therefore be immobilized; at other sites the first therapeutic agent will remain soluble and therefore diffuse away and be rapidly excreted.

See also Rapoport Declaration.
See also Mayers Declaration.

Paper 27, page 5, line 6-10

"... (g') Applicant was invited to submit objective evidence to resolve this issue, no objective evidence has been submitted but Applicant has admitted on the record that 'ultimately, the insoluble precipitate will be removed by convection and phagocytosis but such removal from tumor tissue will be slower than for normal tissues.'"

Paper 27, page 5, line 23 – page 6, line 7

"Dr. Epstein states that insoluble DNA is retained much longer in tumor tissue compared to normal tissue and that one skilled in the art would readily recognize that the insoluble precipitate formed in Dr. Rose's invention will be retained in the same way. The argument has been considered but has not been found persuasive because it is clear that, although retained longer, the insoluble precipitate will be removed. It cannot be determined or predicted from the information in the specification or in the art of record that the invention will function as claimed."

Response 4:

The Publication Exhibits showing the absence of lymphatic drainage and the inhibition of macrophages in the tumor (Publication Exhibits B and C, page 36 submitted with the response filed May 25, 1999), as well as the specification (page 35-36), provide sufficient guidance to enable one skilled in the art to successfully predict, without undue experimentation, that the first therapeutic agent will function as disclosed in the present invention, and that the first extra-cellular precipitate will remain in the tumor tissue longer than normal tissue (i.e. will be removed from tumor tissue more slowly), and furthermore that the first extra-cellular precipitate will remain in the tumor tissue for sufficient time for the present invention to be practiced. For example, trypan blue

adsorbed to albumin (a soluble macromolecule) is retained in tumor tissue for over 5 days, whereas it remains in normal tissue for only a few hours – this difference reflects the fact that normal tissues, but not cancer tissues, have an effective lymphatic drainage. Those skilled in the art would understand that this difference (days in cancer tissues versus hours in normal tissues) would be amplified for insoluble materials. This is confirmed by the long-term retention of insoluble DNA which has been relocated from inside cells to the extra-cellular fluid. While it is true that the extra-cellular precipitate of the present invention will eventually be removed by phagocytosis or convective flow, it need remain in the extra-cellular fluid of the cancer only for a matter of days in order for the present invention to be practiced (see Response 1).

See also Mayers declaration.

Paper 27, page 9, line 14-19

"Applicant argues that the Epstein Declaration addresses the present rejection. The Epstein Declaration states the opinion that the drugs recited in the cited reference are all soluble. The argument has been considered but has not been found persuasive. Applicant was invited to present objective evidence showing that all of the recited prodrugs, when converted into drugs were soluble. No subjective evidence has been submitted."

Response 5:

According to the Merck Index, all of the drugs listed on Page 9 Lines 14-17 of International Publication No. WO 91/19134 dated 27 JUN 1991 are soluble except melphalan, which is insoluble but does not undergo a soluble to insoluble conversion as does the first therapeutic agent of the present invention. Furthermore, it would be expected by one skilled in the art that the recited pro-drugs when converted into active drugs were soluble, because such non-radioactive drugs must be soluble in order to diffuse through the cancer and thus have more than an extremely limited localized effect (i.e. have a "bystander effect"). Furthermore, none of the recited pro-drugs were

therapeutically radioactive, because there is no way to make a therapeutically radioactive pro-drug inherently less toxic than the active drug to which it is converted. Only by causing extended retention time of a radioactive pro-drug (as caused by the soluble-to-insoluble conversion of the first and additional therapeutic agents of the present invention) can the pro-drug be made less toxic than the active drug.

Paper 27, page 9, line 6-9

"Applicant argues claim 79 has been amended to provide a better definition of the invention. The argument has been noted but has not been found persuasive because the amendment did not include the deletion of the indefinite term "derivatives."

Response 6:

Applicant did in fact, in the amendment, include the deletion of the indefinite term "derivatives." The relevant text in the amendment filed January 13, 1997 (pages 3-4) read as follows: "79. (twice amended) A therapeutic agent in accordance with claim 69 in which each of the indoxyl compounds includes benzyloxy compounds [and derivatives of benzyloxy compounds] attached at position 5 of the indoxyl compounds to [alter the solubility, digestibility, color, and physical state] reduce the ability of the indoxyl compounds and the extra-cellular precipitate to move by at least one of diffusion and convective flow in the extracellular fluid."

SUMMARY

It is submitted that the formal objections and rejections to claims 69-83 have been overcome herein.

Therefore, it is submitted that claims 69-83 should now be found to be in condition for allowance.

Favorable action is solicited.

Respectfully submitted,

John Q. McQuillan
Reg. No. 19,805

Dated: November 27, 2000